Angiotensin Receptor Blockers Tied to Ca Risk

BY DIANA MAHONEY

FROM THE LANCET ONCOLOGY

Angiotensin-receptor II blockers are associated with a modestly increased risk of new cancer diagnoses, according to a meta-analysis of randomized controlled trials.

The limited amount of new cancer data in the available literature, however, precludes the calculation of exact cancer risk associated with each individual agent in this class of drugs, wrote lead investigator Dr. Ilke Sipahi and his colleagues at Case Western Reserve University in Cleveland.

VITALS

Major Finding: Patients taking angiotensin receptor blockers had a significantly higher risk of new cancer occurrence (7.2%) than did patients not on ARBs (6.0%), with a risk ratio of 1.08.

Data Source: A meta-analysis of nine randomized controlled trials of ARBs that included data on new cancer occurrence, solid organ cancer occurrence, and cancer deaths.

Disclosures: Study investigators disclosed various financial relationships with Pfizer, AstraZeneca, Ranbaxy, Centocor Research and Development, Cordis/Johnson & Johnson, Daiichi-Sankyo, Medicines Company, Medtronic Vascular, Portola, Schering-Plough, Accumetrics, Sanofi-Aventis, Novartis, and ARCA Biopharma.

Angiotensin receptor II blockers (ARBs) are commonly used for the treatment of hypertension, heart failure, and diabetic neuropathy. Because a number of several large ARB trials have been completed since 2003, when "an unexpected finding" of significantly higher fatal cancers among patients taking the ARB candesartan was observed in a study assessing the drug's efficacy in heart failure (Lancet 2003;362:759-66), Dr. Sipahi and his colleagues designed a meta-analysis of the published randomized controlled trials of drugs in this class to examine their effect on the occurrence of new cancers.

Secondary objectives included the determination of whether ARBs are associated with the occurrence of specific solid-organ cancers and cancer deaths, they wrote.

The meta-analysis included studies published before November 2009 in which an ARB was given in at least one group. Only those studies that enrolled least 100 patients and had a minimum 1 year follow-up were considered, according to the authors. Of the trials that fit these criteria and reported cancer data, five (61,590 patients) had new-cancer data available and were included for the evaluation of the primary outcome of new cancer occurrence. Additionally, for consideration of the secondary outcomes, five trials that reported data on common types of solid organ cancers (68,402 patients) and eight trials that reported data on cancer deaths (93,515) were evaluated, the authors wrote, noting that nine trials were included overall (Lancet Oncol. 2010 [doi:10.1016/S1470-2045(10)70142-6]).

For the primary outcome of cancer recurrence, patients who were randomized to ARB treatment had a 7.2% risk of new cancer occurrence, compared with a 6.0% risk among patients in the control groups, which is a statistically significant difference. An analysis of three of the trials in which cancer was a prespecified end point and cancer data were rigorously collected also showed a significant increase in risk of cancer with ARBs, they wrote.

Because the ARB telmisartan was used as the study drug in 86% of the patients randomized to an ARB, the investigators conducted a meta-analysis of three of the trials looking at this drug, which showed an increase in new cancer occurrence of borderline significance. Analyses looking specifically at patients on background ACE inhibitor therapy and looking at patients without concomitant ACE inhibitor treatment showed significant increases in new cancer occurrences.

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MY TAKE

Dealing With Drug Safety Questions

The meta-analysis linking angiotensin receptor blockers with an increased risk of incident cancer raises crucial drug safety questions.

While the meta-analysis has its strengths—particularly its size, the thoroughness of the literature search, and the application of appropriate filters to exclude potentially unreliable data—there are also important weaknesses, including the study's post hoc nature and the fact that the trials were not designed to explore cancer outcomes," leading the investigators to be "appropriately cautious" in their interpretation of the data.

Until regulators review the possible association between ARB use and cancer and report their findings, "we should use ARBs, particularly telmisartan, with greater caution. ARBs can be reserved for patients with intolerance to ACE inhibitors." Using ARBs more selectively will also save money, "since nearly all ARBs are proprietary while ACE inhibitors are generic."

STEVEN E. NISSEN, M.D., *is chair of the department of cardiovascular medicine at the Cleveland Clinic. His remarks were made in an accompanying commentary (Lancet Oncol. 2010 [doi: 10.1016/S1470-2045(10)70142-X]). He has received research support for clinical trials from Pfizer, Astra Zeneca, Novartis, Novo Nordisk Roche, Daiichi-Sankyo, Takeda, Sanofi-Aventis, Resverlogix, and Eli Lilly. He consults for many pharmaceutical companies, but requires them to donate all honoraria or consulting fees directly to charity.*

the "meta-analysis showed an increase in relative risk for the occurrence of new lung cancer in patients randomized to an ARB compared with control," the authors wrote. "This effect was also seen in the subgroup of patients who received background ACE-inhibitor therapy." While there was an excess of prostate cancer in the ARB groups in all five trials, it was not significant in meta-analysis, they stated.

When evaluating for cancer deaths, the authors wrote, "there was no significant difference in cancer deaths between patients randomized to ARBs and those randomized to control for the duration of the follow-up."

The clinical significance of the "modest but significant" increased risk of new cancer occurrence is unknown, the authors conceded. "The finding of a 1.2% increase in absolute risk of cancer over an average of 4 years needs to be interpreted in view of the estimated 41% lifetime cancer risk," they wrote.

Importantly, because new cancer data were available for only three of seven FDA-approved ARBs, and because most of the patients included in the meta-analysis received telmisartan, "it is not possible to draw conclusions about the exact risk of cancer associated with each particular drug," the authors stated, nor is it known whether the remaining four ARBs are associated with an increased risk of new cancers.

The mechanism for the possible increase in new cancer occurrences associated with ARBs is uncertain, according the authors. Although experimental studies using cancer cell lines and mouse models have implicated the renin-angiotensin system in the regulation of cell proliferation, tumor growth, angiogenesis, and metastasis, and evidence shows that both angiotensin II type-1 blockade with ARB and direct stimulation of angiotensin II type-2 are capable of stimulating tumor angiogenesis in vivo, the authors wrote, "the relevance of these observations in human malignancy is largely unknown."

Although the findings of this study are limited by the fact that the pooled results come from trials not designed to explore cancer outcomes as the primary end point and by the lack of individual patient level cancer data, "meta-analysis can be useful in providing insights into issues of safety and rare adverse events that might provide the hypothesis for a prospective trial," the authors wrote, noting that the findings "warrant further investigation." ■